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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/766,642	01/28/2004	Anthony Atala	105447-2	4621
21125 7590 10/10/2007 NUTTER MCCLENNEN & FISH LLP WORLD TRADE CENTER WEST 155 SEAPORT BOULEVARD BOSTON, MA 02210-2604			EXAMINER FORD, ALLISON M	
			ART UNIT 1651	PAPER NUMBER
			NOTIFICATION DATE 10/10/2007	DELIVERY MODE ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

doctet@nutter.com

Office Action Summary

Application No.

10/766,642

Applicant(s)

ATALA ET AL.

Examiner

Allison M. Ford

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 16 July 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-4, 6-12, 23-26, 28, 29 and 33-37 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-4, 6-12, 23-26, 28, 29 and 33-37 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

Request for Continued Examination

Applicants' Request for Continued Examination was received 16 July 2007 and has been entered into the application file. Claims 1 and 23 have been amended; claims 5, 13-22, 27 and 30-32 are cancelled; new claims 33-37 have been added as new. Claims 1-4, 6-12, 23-26, 28-29 and 33-37 remain pending in the instant application, all of which have been considered on the merits.

Response to Arguments/Amendments

Applicants' arguments submitted on 16 July 2007 have been fully considered. Applicants have amended claim 1 to clarify the claim language, the objection is therefore withdrawn.

In response to the rejection of claims under 35 USC 103(a) Applicants have argued that the examiner has improperly used hindsight to reconstruct Applicants' invention. Applicant further submits that none of the cited references teach or suggest encapsulating the transfected cells, as is now required by the claims, and thus the amendment obviates the rejection of record.

Applicants' arguments have been fully considered, but are moot in view of the new grounds of rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-4, 6-12, 23-26, 28-29 and 33-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Naughton et al, (US 2003/0007954), in view of Atala (US Patent 6,479,064), MacLaughlin et al (US Patent 6,692,738), Springer et al (J Gene Med, 2000), Rinsch et al (Gene Therapy, 20001) and Penn et al (US 2004/0161412 A1, as fully supported by provisional applications 60/405274 & 60/424065).

Applicants amended claim 1 is directed to a method of organ augmentation comprising transiently transfecting a first population of cells with a plasmid encoding angiogenesis modulating agent VEGF; encapsulating the transfected cells; selecting a second population of cells, wherein the second population of cells comprises cells of a different cell type than the first population; suspending the first and second population of cells in an injectable polymer matrix; injecting the polymer matrix into a target tissue region where the first population of cells will express the VEGF; thereby inducing assimilation and differentiation of at least one of the populations of cells in the target region and augmenting organ function. Claim 2 requires the transiently transfected cells to produce the angiogenesis modulating agent for less than three weeks. Claim 3 requires the first population of cells to comprise undifferentiated cells. Claim 4 requires the first population of cells to comprise vascular endothelial cells. Claim 6 requires the second population of cells to comprise undifferentiated cells. Claim 7 requires the second population of cells to comprise vascular endothelial cells. Claim 8 requires the polymer matrix to comprise collagen; claim 8 requires the collagen to be type I collagen. Claim 10 requires first population of cells to express the angiogenesis modulating agent for less than about 10 weeks. Claim 12 requires the first population of cells to comprise myoblasts. Claim 34 requires the step of encapsulating the transfected cells to be encapsulated in microcapsules; claim 35 requires the transfected cells to encapsulated in alginate-PLL capsules.

Applicant's amended claim 23 is directed to a method for augmenting organ function, comprising culturing at least a first population of cells on a matrix material to produce an organ construct; transiently transfecting a second population of cells with a plasmid encoding an angiogenesis modulating agent, wherein the second population of cells comprises cells of a different cell type than the first population, and wherein either the first or second population of cells comprises myoblasts; encapsulating the transfected cells; and implanting the organ construct and the transfected cells *in vivo* at one target site to replace or augment organ function; wherein the transfected cells express the angiogenesis modulating agent for less than about 3 weeks. Claim 24 requires the matrix to be decellularized tissue. Claim 25 requires the matrix to be a hydrogel. Claim 26 requires the matrix to be a polymer. Claim 28 requires the angiogenesis modulating agent to be VEGF. Claim 29 requires the method to further comprise assimilating the transfected cells into a tissue layer. Claim 33 requires the organ construct and the transfected cells to be implanted at a plurality of target sites *in vivo*. Claim 36 requires the step of encapsulating the transfected cells to be encapsulated in microcapsules; claim 37 requires the transfected cells to be encapsulated in alginate-PLL capsules.

At the time the invention was made the need for effective methods of reconstructing and repairing ischemic tissues was well recognized in the art (See, e.g. Naughton et al, page 1). It is the opinion of the Office that Applicants' current claimed methods are a combination of several treatment methods each individually taught in the prior art. Absent a showing that the claimed combination of treatment methods produces unpredicted results, it is respectfully submitted that the combination of multiple treatment methods, each intended to reconstruct and repair ischemic tissue and to promote angiogenesis therein, would have been obvious to one of ordinary skill in the art at the time the invention was made. It has been held that when there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions (in the instant case the 'solutions' would be the treatment

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methods), a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. See *KSR International Co v Teleflex 82 USPQ2d 1385 (US 2007)* at page 1397.

A first treatment method taught in the prior art for repairing ischemic tissue, particularly ischemic myocardial tissue, involves implantation of tissue engineered stromal tissue adjacent to the ischemic tissue to promote new cellular growth and angiogenesis in the ischemic tissue. Naughton et al is relied upon:

Naughton et al teach a method for treatment of ischemic tissue, particularly myocardial ischemia, by producing and implanting a three-dimensional stromal tissue construct to the ischemic region of the heart to promote vascularization of the heart and regeneration of the damaged cardiac muscle cells (which applicant calls organ augmentation) (See Naughton et al, Pg. 2, paragraph 0028). The method of Naughton et al comprises formation of a three-dimensional stromal tissue construct by inoculating stromal cells onto a three-dimensional scaffold; and then implantation of the three-dimensional tissue construct at various locations where the heart tissue was damaged by ischemia so as to allow assimilation of the stromal cells into the natural cardiac tissue (See Naughton et al, Pg. 5, paragraphs 0055-0057). It would further have been obvious to one of ordinary skill in the art, at the time the invention was made, to implant multiple tissue constructs at multiple sites, as needed to correct ischemic damage. One would be motivated to produce and implant as many tissue constructs as needed to correct all areas of ischemic damage in order to fully treat a patient.

Regarding the material of the three-dimensional scaffold (matrix), Naughton et al teach the three-dimensional scaffold can consist of PGA, collagen, polylactic acid (a polymer) or hyaluronic acid (See Naughton et al, Pg. 2, paragraph 0032). Though Naughton et al implant a three-dimensional 'organ construct' into the target tissue area, at the time the invention was made it was well known that various

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substrate materials and forms could be successfully utilized for delivery of cells to a target tissue region for assimilation into the target tissue. In support, MacLaughlin et al and Atala et al are referenced. MacLaughlin et al discusses the three main types of matrices: microfabricated devices, fibrous scaffolds (such as that of Naughton et al), and injectable hydrogels; more specifically, with regards to hydrogels, MacLaughlin et al disclose various polymeric materials, including collagen, which are used as the injectable hydrogel materials (See MacLaughlin et al, abstract & col. 7-14). Similarly, Atala et al also disclose various matrix materials and forms which are commonly used in the field of tissue engineering and cell delivery, including hydrogels and decellularized tissue (See, e.g. Atala, Pg. 1, paragraph 0012). Therefore, at the time the invention was made different matrix material and forms were recognized as suitable for delivery of cells to the body for purposes of tissue engineering and augmentation of existing tissues within the body; thus, though Naughton et al utilize pre-formed scaffold frameworks, it would have been obvious to the skilled artisan to alternatively use alternative scaffold forms, including injectable polymeric hydrogels, including type I collagen, or decellularized tissue, as the matrix material for culture and delivery of the cells, and use of these various other forms would be expected to yield the same result (successful delivery of the cells to the target tissue site). Substitution of one element for another known in the field is considered to be obvious, absent a showing that the result of the substitution yields more than predictable results. See *KSR International Co. v Teleflex Inc* 82 USPQ2d 1385 (US 2007) at page 1395.

Regarding the types of cells cultured on the three-dimensional scaffold Naughton et al teach the stromal cell populations can comprise fibroblasts as well as tissue specific cells, such as heart cells, particularly cardiac muscle cells and aortic smooth muscle cells (See Naughton et al, Pg. 3, paragraph 0034 & claims 3 and 4). Additional cells can be added to form the three-dimensional tissue, including endothelial cells (See Naughton et al, Pg. 3, paragraph 0038). It would have been obvious to one of ordinary skill in the art to additionally include endothelial cells, particularly vascular endothelial cells, in

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the three-dimensional tissue construct of Naughton et al because at the time the invention was made, inclusion of vascular endothelial cells, in addition to stromal/parenchymal cells, in tissue engineered constructs was known to promote formation of a primitive vascular system (See Atala, col. 2, ln 19-52). Thus, because one of the goals of the tissue construct of Naughton et al is to promote vascularization in the tissue construct, one would be motivated to include the vascular endothelial cells which were known to promote such vasculogenesis (See Naughton et al, Pg. 1, paragraph 0007). Thereby, upon implantation of the tissue construct, Naughton et al effectively co-administers both the stromal cells, which may comprise myoblasts and other tissue specific cells, as well as vascular endothelial cells.

A second treatment method taught in the prior art for repairing ischemic tissue involves implantation of encapsulated cells which have been genetically engineered to express angiogenesis modulating agents, such as VEGF or FGF-2, so to improve survival and vascularization at the implantation site. Springer et al and Rinsch et al are each relied upon:

Springer et al discloses a method wherein myoblasts transfected to express VEGF are encapsulated in alginate-PLL microcapsules and then injected either subcutaneously or into the peritoneal cavity to promote blood vessel formation (See Springer et al, Pg. 280, col. 2). Springer et al report that, unlike non-encapsulated cells (their previous work) the encapsulated cells led to blood vessel formation and recruitment of endothelial and smooth muscle cells (See Springer et al, pg. 286, col. 2 – Pg. 287, col. 1).

Rinsch et al disclose a method for promoting revascularization and healing of ischemic skin tissue. Their method involves implanting encapsulated, genetically engineered myoblasts, wherein the myoblasts were transfected with VEGF or FGF-2 (See Rinsch et al, Pg. 524, col. 1), under the ischemic zone at the time of implantation of a transplanted skin flap. In tissues wherein cells expressing FGF-2

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were implanted, Rinsch et al report decreased necrosis (See Rinsch et al, Pg. 526, Table 2). Rinsch et al report formation of blood vessels around the implanted capsules (see Rinsch et al, pg. 526, col. 2).

While both Springer et al and Rinsch et al report increased recruitment of endothelial cells and muscle cells and Nuevo-blood vessel formation, both Springer et al and Rinsch et al also note that constituent expression of the angiogenesis modulating genes can produce deleterious results, so they suggest using transfection methods whereby the gene expression can be controlled (See Springer et al, Pg. 287, col. 1-2) or halting treatment after revascularization (See Rinsch et al, Pg. 524, col. 1). Following Springer et al's suggestion, it would have been obvious to one of ordinary skill in the art to use myoblasts which will transiently express the angiogenesis modulating gene(s); such methods were known in the art, see Penn et al.

Penn et al teach transfecting a population of skeletal myoblasts with a VEGF expression vector by plasmid DNA transfection (See Penn et al, Pg. 7, paragraph 0092). Penn et al also teach that the VEGF can be transiently expressed for any suitable and defined length of time (See Pg. 8, paragraph 0100-0102). Penn et al teach that local and transient expression of VEGF is sufficient to induce neovascularization and minimize systemic effects and hemangioma formation (See Penn et al, Pg. 1, paragraph 0004). With regards to the length of time the VEGF is produced, Penn et al teach that the duration of the transient expression is a result effective variable that would be routinely optimized by one of ordinary skill in the art (See Penn et al, pg. 8, paragraphs 0099-0102). Penn et al teach that the cells can be transiently transfected so as to express a therapeutic amount of VEGF; Penn et al further teaches that it is well within the scope of one skilled in the art to determine the appropriate therapeutic amount on an individual basis, as factors such as size, age, sex, presence of other drugs, and concentration of the active drug, all effect the optimal duration of expression. Therefore, the duration of the transient expression of VEGF would have been routinely optimized by one of ordinary skill in the art at the time the invention was made, especially with lack of evidence to the contrary, submitting the claimed time

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period is critical. Penn et al further add that their cells, which transiently express VEGF, are useful to stimulate cell differentiation and regenerate ischemia damaged tissue (See Penn et al, Pg. 2, paragraph 0020 & Pg. 3, paragraphs 0044-0045). Therefore, at the time the invention was made, the benefits of transiently transfected cells, compared to constitutively transfected cells, was recognized in the art, and methods for producing such transiently transfected cells were known. Thus, in order to provide optimal and controlled delivery of the angiogenesis modulating agents, it would have been obvious to the artisan of ordinary skill to encapsulate transiently transfected cells in the methods of Springer et al and/or Rinsch et al.

Therefore, it is submitted that combining the therapies of implanting new engineered tissue to sites of ischemic tissue (disclosed by Naughton et al) and delivering microcapsules containing cells genetically engineered to transiently express angiogenesis modulating agents to sites of ischemic tissue (disclosed by Springer et al and Rinsch et al, taken in view of Penn et al) into a single method would have been obvious to one of ordinary skill in the art at the time the invention was made. Based on the recognized need to find an effective treatment for revascularizing ischemic tissue, one of ordinary skill in the art would have been motivated to try to combine known therapies to develop a more effective solution for the known problem, as a person with ordinary skill has good reason to pursue the known options within his or her technical grasp. See *KSR International Co v Teleflex Inc*, (cited *supra*) at page 1398. Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

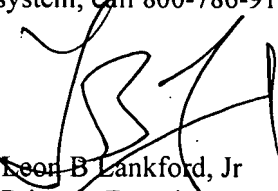
Conclusion

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Allison M. Ford whose telephone number is 571-272-2936. The examiner can normally be reached on 7:30-5 M-Th, alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



Leon B Lankford, Jr
Primary Examiner
Art Unit 1651